REMARKS

Claim 1-20 are currently pending in the application. In order to advance prosecution, Applicants have cancelled claims 5-6, 9-10, and 13-20. Cancellation of these claims makes no admission regarding the patentability of this subject matter and should not be so construed. Applicant reserves the right to pursue this subject matter in this or in any other appropriate patent application.

The amendments to the pending claims were made to clarify the scope of coverage and more particularly point out and distinctly claim the present invention. These amendments are made without prejudice, do not constitute amendments to overcome any prior art rejections under U.S.C. § 102, and do not present any new matter.

Replacement Figures 1-38 have been amended to comply with C.F.R. § 1.84. Specifically, the lines, numbers, reference characters, and margins have been changed so that they comply with the rules and the comments on the Draftsperson's report. No new matter has been introduced by any of these amendments to the Figures.

Discussion of the Election/Restriction Requirement

The Office Action of October 2, 2002 required a restriction under 35 U.S.C. § 121. In response, Applicants elected Group II with traverse. The Office Action of October 2, 2002 acknowledged that claims 1-4 link inventions I and II. Therefore, Applicants reiterate their understanding that upon allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claims(s) depending from or otherwise including all of the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. The Office Action of February 27, 2002 alleges that Applicants traversal is

not found persuasive because there are no allowable linking claims. However, the present rejections are either overcome or traversed below, and therefore Applicants respectfully request the examination of the linked inventions in the instant application.

Further, the Office Action of October 2, 2002 required the election of a species of the claimed invention under 35. U.S.C. § 121. In response, Applicants elected the species α2,6-ST glycosyltransferase for initial prosecution with the understanding that upon allowance of a generic claim, the Office will consider the additional species dependant from the allowed generic claims. The Office Action of February 27, 2002 alleges that the additional species will not be considered because there are no allowable generic claims. However, the present rejections are either overcome or traversed below, and therefore Applicants respectfully request the examination of additional species dependant from the allowed generic claims in the instant application.

Discussion of the 35 U.S.C. § 112, ¶ 1 Rejection (Enablement)

Claims 1-4, 7-8, and 11-12 are rejected under 35 U.S.C. § 112, first paragraph because allegedly the specification does not reasonably provide enablement for a method of decreasing the tumorgenicty or malignancy of a brain cancer cell. This rejection is respectfully traversed.

Under 35 U.S.C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, to enable claims 1-4, 7-8, and 11-12, the specification must teach one skilled in the art how to make and use a method of *decreasing* the tumorigenicity or malignancy of a brain cancer cell, comprising altering the expression of a glycosyltransferase within the cell. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2)

from the disclosures in the application coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Teletronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

Contrary to the Office Action's allegation, the specification provides considerable guidance to enable a skilled artisan to make and use a method of decreasing the tumorigenicity or malignancy of a brain cancer cell comprising altering the expression of a glycosyltransferase within the cell. For example, the specification teaches how to transfect brain cancer cells with exogenous DNA encoding a glycosyltransferase, which results is a decrease in the tumorigenicity or malignancy of the cancer cells. The specification teaches how to transfect human glioma cells with α2,6-ST glycosyltransferase cDNA, which results in an increase in glycosyltransferase activity within the cell. *Specification* at 33-38. In addition, the specification teaches that transfection of the α-2,6-ST glycosyltransferase gene into glioma cells caused a marked inhibition of glioma cell invasivity and a significant reduction in adhesivity to the extracellular matrix molecules, fibronectin and collagen. *Id.* at 38-41. Furthermore, α3ß1 integrin was found to contain α2,6-linked sialic acids, and tyrosine phosphorylation of $p125^{fak}$ was blocked despite increased expression of $p125^{fak}$ message. *Id.* at 41-46. Moreover, when these transfected cells were either subcutaneously implanted into the hind-flank of mice or were injected stereotactically into the right basal ganglia of mice, the cells demonstrated a decrease in tumorigenicity as compared to the parent cells or cells transfected with vector alone. *Id.* at 46-48.

In addition, the specification teaches how to make and use vectors for delivery of nucleic acids encoding glycosyltransferases. For example, the specification teaches how to construct an adenoviral vector encoding the α2,6-ST glycosyltransferase gene. *Id.* at 57-59. In addition, the

specification teaches how to use the constructed vector to transfect brain cancer cells. *Id.* at 59-60. Further, the specification teaches how to make additional vectors for the delivery of glycosyltransferase into brain cancer cells, such as, but not limited to, the use of adenoviral vectors, adeno-associated viruses, Herpes simplex virus type-1, vaccinia virus, and retroviral vectors. *See id.* at 15-17. Moreover, the specification additionally teaches non-viral nucleic acid delivery techniques, including, but not limited to, DNA-ligand complexes, adenovirus-ligand-DNA complexes, direct injection of DNA, $CaPO_4$ precipitation, gene gun techniques, electroporation, and lipofection. *See id.* at 17.

Further, the specification teaches how to use nucleic acids encoding glycosyltransferases for decreasing the tumorigenicity or malignancy of a brain cancer cell *in vivo*. For example, the specification teaches the stereotactic injection of a recombinant adenoviral vector comprising a nucleic acid encoding α2,6-ST glycosyltransferase under the transcriptional control of the human CMV immediate-early enhancer/promoter into an established tumor in a rat brain. *Id.* at 60-61. In addition, the specification teaches how to decrease the tumorigenicity of brain cancer cells in humans following the surgical resection of a tumor. *Id.* at 61-62.

Despite these teachings, the Office Action alleges that the invention is not enabled because the specification does not provide any examples wherein the brain cancer of any animal was decreased as a result of treatment with a nucleic acid encoding glycosyltransferases. Contrary to the Office Action's allegation, the specification does teach that treatment with nucleic acids encoding glycosyltransferases does result in a decrease of tumorigenicity or malignancy of a brain cancer cell. For example, the specification teaches the transfection of human brain cancer cell line U373 MG with α2,6-ST cDNA. In addition, the specification teaches the implantation of this cell line into a mouse, resulting in a decrease in tumorigenicity

and malignancy. Notwithstanding the fact that the specification does provide evidence that the tumorigenicity and malignancy of a brain cancer cell is decreased by the claimed method, compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph does not, in fact, turn on whether an example is disclosed. M.P.E.P. § 2164.02. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 164 U.S.P.Q. 642 645 (C.C.P.A. 1970); M.P.E.P. § 2164.02. Applicants submit that, based on teachings and examples relating to, *inter alia*, the transfection of nucleic acids encoding glycosyltransferases, one skilled in the art would have known how to alter the glycosyltransferases activity within the cell such that the tumorigenicity or malignancy of the brain cancer would be decreased.

The Office argues that "gene therapy is considered a highly experimental area of research," and that "no cures can as yet be attributed to gene therapy." The test, however, established by the Federal Circuit, for correlating *in vitro* data and a claimed method of use is that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate*. M.P.E.P. § 2164.02 (emphasis added); *se In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Also, "[a] rigorous or an invariable exact correlation is not required" to enable a pharmacological invention. M.P.E.P. § 2164.02; *see Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). As further support for this position, the Federal Circuit has found that data showing the successful use of compounds as anti-tumor substances in tumor model systems were sufficient to enable the use of compounds as anti-cancer drugs in animals. *Brana*, 34 U.S.P.Q.2d at 1436. Moreover, therapeutic inventions do not preclude "the expectation of further research

and development;" for example, FDA approval is not a prerequisite for patent protection. *Brana*, 34 U.S.P.Q.2d at 1442-43.

In the present case, as discussed above, the specification clearly teaches the successful transfer of the α2,6-ST glycosyltransferase into a brain cell in cell culture. Further, the specification clearly teaches the successful transplantation of the transfected cells into a mouse model. One of ordinary skill in the art would have recognized that appropriate cell cultures models and mice models as predictive models for DNA delivery and activity *in vivo*. Thus, in the absence of any evidence that the current model does not correlate, the specification is enabled for providing the altering of expression of a glycosyltransferase to a cell *in vivo*.

Despite these teachings, the Office Action alleges that the treatment of cancer is considered highly unpredictable, and that future treatment strategies will likely involve synergistic combinations of agents. Contrary to the Office Action's assertion, however, the specification does provide guidance for methods that *decrease* the tumorigenicity and malignancy of brain cancer cells, as described above. The Office Action's allegation appears to be that because the teachings in the specification *may not cure* brain cancer, that the claimed invention is not enabled. However, it is not necessary that applicants enable a cure for brain cancer; rather the present claims merely require a *decrease* in tumorigenicity and malignancy of the brain cancer cells. Thus, a person skilled in the art to which the present invention pertains would understand that the specification teaches how to decrease the tumorigenicity or malignancy of a brain cancer cell by altering the expression of a glycosyltransferase within the cell.

Further, the Office Action cites Rosenberg *et al*, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287 (5461):2163-5, 2000, Anderson W.F., Nature

392:25-30, 1998, Verman *et al* Nature, 389:239-242, 1997, and Touchette, Nat. Med. 2(1) 7-8, 1996, for the proposition that gene therapy is considered to be a highly experimental area of research, and that no *cures* can yet be attributed to gene therapy. In the absence of any technical reasons as to why the described methods would not work, these articles are insufficient to establish a *prima facie* case of lack of enablement. In fact, these articles cited by the Office Action provide numerous examples of clinical trials utilizing gene therapy, thereby establishing that gene therapy techniques were well known to those skilled in the art. Although FDA approval is not required to obtain patent protection for pharmaceutical inventions, it does provide further confirmation that those skilled in the art, as well as the regulatory authority, accept the therapeutic uses of gene therapy. This acceptance for gene therapy is demonstrated by the FDA's approval of the numerous clinical trial cited in these references. Therefore, the therapeutic use of gene therapy for altering the expression of a glycosyltransferase in a brain cancer cell would not require undue experimentation by those of ordinary skill in the art based on the guidance provided in the instant specification and from the work done on the wide range of targets, cell types, and diseases described in the cited references.

Finally, the Office Action alleges that it would require undue experimentation to determine how to decrease the tumorigenicity or malignancy of a brain cancer cell. In this regard, the law clearly states that "a considerable amount of experimentation is permissibly, if it is merely routine." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he mere fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-Charge Cell Cultur Microcarriers*, 221 U.S.P.Q. 1165 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985); M.P.E.P. § 2164.01.

Therefore, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); M.P.E.P. § 2164.01. As discussed above, using the teachings in the specification, one skilled in the art could alter the expression of a glycosyltransferase within said cell. Thus, even if one skilled in the art would require some experimentation to practice the present invention, the experimentation would be merely routine, and would not constitute undue experimentation.

For the reasons set forth above, the specification satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection be withdrawn.

Discussion of the 35 U.S.C. § 112, ¶ 1 Rejection (Written Description)

Claims 1-4, 7-8, and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Claims 1-4, 7-8, and 11-12 recite methods for decreasing the tumorigenicity and malignancy of a brain cancer cell by altering the glycosyltransferase activity within the cell. The Office Action asserts that the specification as filed only discloses the transfection of a human glioma cell line U-373MG with a recombinant adenoviral vector comprising nucleic acid encoding α2,6-ST. In addition, the Office Action contends that the specification fails to disclose a method of increasing glycosyltransferase activity by administering any exogenous protein or any chemical agents. The Office Action concludes that one skilled in the art would conclude that applicants were not in the possession of the methods for decreasing the tumorigenicity or malignancy of brain cancer cells.

The written description requirement is *separate and distinct* from the enablement requirement. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q. 111, 1114 (Fed. Cir. 1991). To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., id.* at 1116; M.P.E.P. § 2163(I). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163(I)(A) (citing *In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); M.P.E.P. § 2163.04. Therefore, the Office must have a reasonable basis to challenge the adequacy of the written description and has the initial burden of presenting, by a preponderance of the evidence, why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *See, e.g., In re Wertheim*, 191 U.S.P.Q. 90 (C.C.P.A. 1976); M.P.E.P. § 2163.04.

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. M.P.E.P. § 2163(I). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or couples with a known or disclosed correlation between structure and function; and (5) the method of making the claimed invention. *Id.* at (II)(A)(2)-(3)(a). Disclosure of *any* combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of

the claimed species is sufficient. *Id.*; *see Reagents of the Univ. Of Calif. v. Eli Lilly*, 43 U.S.P.Q.2d 1398. Correspondingly, as the Patent Office's internal guidelines assert, "the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function." M.P.E.P. § 2163(II)(A)(3)(a)(i)(C)(2). Thus, when "knowledge and level of skill in the art is high, a written description question *should not be raised* for original claims even if the specification discloses only a method of making the invention and the function of the invention." *Id.* (emphasis added), *see In re Hayes Microcomputer Products, Inc. Patent Litigation*, 25 U.S.P.Q.2d 1241 (Fed. Cir. 1992) ("An applicant's disclosure obligation varies according to the art to which the invention pertains.").

Contrary to the Office's allegation, the specification as filed thoroughly describes the requisite identifying characteristics of altering the expression of a glycosyltransferase within a brain cancer cell. The Office action contends that the invention is not described by alleging that the specification fails to teach any specific exogenous protein or any chemical agent that increases the bioactivity or increases the transcriptional regulation of a specific glycosyltransferase synthesis. Without conceding this allegation, the Office Action fails to present evidence why a person skilled in the art would not recognize in the disclosure that the Applicants were in possession of methods for decreasing the tumorigenicity or malignancy of a brain cancer cell as claimed. As outlined above, the claimed method is clearly and thoroughly described by its structure and function for the expression of glycosyltransferases with a brain cancer cell. Thus, the Office Action seems to suggest that the specification lacks adequate written description because the specification only disclosed the transfection of a human glioma cell line with α2,6-ST glycosyltransferase with a recombinant adenoviral vector.

Notwithstanding the fact that the specification disclosures additional working examples of the invention, including the transfection of a human glioma cell line with α2,6-ST glycosyltransferase with a cationic liposome system, as well as the implantation of this cell line into mice, the written description requirement does *not* require an actual reduction to practice. M.P.E.P. § 2163(II)(A)(3)(a). In other words, the specification need not actually include working examples to satisfy the written description requirement. However, as stated above, the specification not only provides the working example acknowledged by the Office Action, the specification contains several working examples of the claimed invention.

The Office Action also asserts that the specification fails to disclose a single inducible promoter that regulates the glycosyltransferase gene expression. The internal rules at the Patent Office, however, clearly state that "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." M.P.E.P. § 2163(II)(A)(3)(a) (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986)). "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *Id.* In the present case, however, the specification does teach transcriptional regulatory regions suitable for use in the present invention, including but not limited to, the human cytomegalovirus (CMV) immediate-early enhancer/promoter, the SV40 early enhancer/promoter, the JC polymavirus promoter, and the chicken ß-actin promoter coupled to the CMV enhancer.

Based on the forgoing discussion, the claimed methods are fully described in the specification such that one skilled in the art would recognize that the Applicants were in possession of methods for decreasing the tumorigenicity or malignancy of brain cancer cells at

the time of filing of the application. In compliance with current case law and the M.P.E.P., the specification describes sufficient relevant identifying characteristics of the claimed invention. In addition, the application provides detailed examples of the claimed invention, further evidencing Applicants' possession of the claimed methods. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, first paragraph rejection.

Discussion of the 35 U.S.C. § 112, ¶ 2 Rejection

Claims 1-4 and 7-8 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants have overcome this ground of rejection. With respect to claims 1 and 7-8, the Office Action stated that the claims are indefinite because they recite the limitation of altering increasing the activity of a glycosyltransferase. Although Applicant respectfully disagrees with the rejection of claims 1 and 7-8, and believes these claims are fully in compliance with § 112, nevertheless Applicants have amended claims 1 and 7-8, and respectfully contend that these amendments overcome the asserted ground of rejection.

In addition, with respect to claim 1, the Office Action stated that it lacks sufficient antecedent basis for the limitation "said altered pattern". In addition, with respect to claim 7, the Office Action stated that it lacks sufficient antecedent basis for the limitation "said altered pattern". Finally, with respect to claim 8, the Office Action stated that it lacks sufficient antecedent basis for the limitation "said altered pattern". In this regard, Applicant has amended claims 1, and 7-8 to better clarify the invention. Applicants respectfully contend that these amendments overcome the asserted ground of rejection.

Discussion of the 35 U.S.C. § 102 Rejection

Claims 1-3 and 7 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Yamamoto *et al.* (Proc. Annu. Meet. Am. Assoc. Cancer Res., 37:63, A436 (March 1996)) ("Yamamoto"). This rejection is respectfully traversed.

Under 35 U.S.C § 102, a claim is anticipated only is each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 2 U.S.P.Q.2d 1051, 1053 (Fed Cir. 1987)' M.P.E.P. § 2131. The single prior art reference must disclose the claimed invention identically and in as complete detail as is contained in the claim. M.P.E.P. § 2131; *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989).

Furthermore, the prior art reference must provide an enabling disclosure. M.P.E.P. §2121.01; *In re Hoeksema*, 399 F.2d 269 (CCPA 1968) ("In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention' 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure' . . ."). It is well-established by the Federal Circuit that "even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000) (quoting *In re Donohoe*, 766 F.2d 531, 533 (Fed Cir. 1985); see also *Ex parte Thomsom*, 24 USPQ2d 1618 (Fed. Cir 1992); *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, USPQ 649 (Fed. Cir. 1986); *Azko N.V. v. U.S. International Trade Commission*, 1 USPQ2d 1241 (Fed Cir. 1986); *In re Borst*, 345 F.2d 851, 855 (CCPA 1965); *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962) (the mere description of an invention is not necessarily an "enabling" disclosure; such descriptions must be capable of placing the invention in the possession of those skilled in the art). A disclosure is enabling if a person of ordinary skill in the art could have made or obtained the claimed invention without an

undue amount of experimentation. *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000) (citing *In re Sheppard*, 339 F.2d 238, 242 (CCPOA 1981).

In other words, a reference "must sufficiently describe the claimed invention to have placed the public in possession of it." *In re Donohue*, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). Therefore, even though a disclosure may be in a written publication, it will not be sufficient prior art if it is not enabling. *Id.*

The Office Action states that Yamamoto teaches a method of decreasing the tumorigenicity or malignancy of brain cancer in vitro by α2,6-ST gene transfection. However, the Yamamoto reference is a single paragraph abstract that does not provide any details as to what specific genetic material was transfected into the cells, nor does it disclose any methodology whatsoever for transfecting the genetic material into the cells. Rather, Yamamoto is limited to a mere mention that a gene was transfected into human glioma cells without any further description. In the absence of any guidance whatsoever, an ordinary skilled artisan would not have known what genetic material could be transfected into a brain cancer cell that would result in an alteration of the glycosyltranferase activity within the cell without undue experimentation. Thus, the Yamamoto publication did not place the public in possession of the instantly claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Discussion of the Claim Objections

Claim 1 is objected to because it recites the limitation "activity of glycosyltransferase". In addition, claims 2-4, 7-8, and 11-12 are objected to because they recite "A method" in line 1.

Applicant has amended the above-referenced claims, thereby overcoming the Office Action's objections.

Claims 8 and 12 are objected to because they contain non-elected species of glycosyltransferase. However, Applicants understand that upon allowance of a generic claim, the Office will consider the additional species dependant from the allowed generic claims. Therefore, Applicants respectfully request removal of this rejection.

Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

Date: August 24, 2003

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